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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary	Application No.	Applicant(s)	
	10/751,072	EYCKERMAN ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,11,13,16,22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,11,13,16,22 and 24-26* is/are rejected.

7)☒ Claim(s) *1,22 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 10/5/07 has been entered in full. Claims 1 and 22 are amended. New claims 24-26 are added. Claims 2, 9, 10, 12, 14, 15, 17-21 and 23 were canceled previously. Claims 1, 3-8, 11, 13, 16, 22 and 24-26 are under consideration.

Note

On page 8 of the 10/5/07 response, Applicants refer to Ihle *et al*, (1995. Trends Genet. 11(2): 69-74) and state that it was "submitted in and [*sic*] IDS field [*sic*] May 16, 2007". However, there is no IDS in the instant application filed on 5/16/07. Applicants may refer to an IDS filed on 5/16/07 in co-pending application 10/303,157. A copy of Ihle *et al*, and a PTO-892 (Notice of References Cited) with the corresponding citation, are attached to this Office Action to make this reference of record in the instant case.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 11, 13, 16, 22 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(1) a recombinant receptor comprising an extracellular ligand-binding domain of a mammalian receptor; a cytoplasmic domain comprising a domain derived from a cytoplasmic domain of a mammalian receptor, at least one activation site that is a tyrosine residue, and a heterologous bait polypeptide heterologous to the domain derived from a cytoplasmic domain of a mammalian receptor; wherein said cytoplasmic domain comprises a JAK-binding site; and wherein the activation of said recombinant

receptor is inhibited by binding of a fusion protein to said bait polypeptide, said fusion protein comprising a prey polypeptide and an inhibitor of the activation of said recombinant receptor that is selected from the group consisting of a member of the SOCS family, a JAK phosphatase, and a STAT phosphatase, and

(2) vectors and cells encoding said receptor;

does not reasonably provide enablement for

(1) a recombinant receptor comprising an extracellular ligand-binding domain of a mammalian receptor; a cytoplasmic domain comprising a domain derived from a cytoplasmic domain of a mammalian receptor, at least one activation site and a bait polypeptide heterologous to the domain derived from a cytoplasmic domain of a mammalian receptor; wherein said cytoplasmic domain comprises a JAK-binding site; and wherein the activation of said recombinant receptor is inhibited by binding of a fusion protein to said heterologous bait polypeptide, said fusion protein comprising a prey polypeptide and at least one of an inhibitor of the activation of said recombinant receptor and a recruitment site for the inhibitor of the activation of said recombinant receptor;

(2) vectors and cells encoding said receptor; or

(3) a recombinant transmembrane receptor, comprising a cytoplasmic domain comprising an intracellular domain derived from a mammalian receptor, a bait polypeptide and an activation site, and a JAK-binding site, wherein an interaction of a prey polypeptide with the bait polypeptide prevents the activation site from activating the recombinant transmembrane receptor, wherein said prey polypeptide comprises an inhibitor selected from the group consisting of a member of the SOCS family, a JAK phosphatase and a STAT phosphatase; and an extracellular domain having a ligand binding domain derived from a mammalian receptor, wherein binding of a ligand to the ligand binding domain activates the recombinant transmembrane receptor upon disruption of the interaction between the prey polypeptide and the bait polypeptide; and wherein the bait polypeptide is heterologous to the intracellular domain.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was set forth previously at pg 2-10 of the 4/5/07 Office Action; new claims 24-26 are herewith included.

Applicants' arguments (10/5/07; pg 5-7), and the amendments to the claims, have been fully considered and are found persuasive in part. The rejection has been maintained but the scope of enablement is modified as set forth herein in view of Applicants' arguments, and the amendments to the claims. It is believed that all of Applicants' arguments are addressed below in the restated rejection.

The nature of the invention is a recombinant receptor for use in screening for a molecule that disrupts an interaction between a bait and a prey molecule. The claimed receptor comprises a ligand-binding extracellular domain (ECD) from a mammalian receptor and a cytoplasmic domain with at least three parts: (1) a cytoplasmic domain from a mammalian receptor; (2) at least one activation site and (2) a heterologous bait polypeptide; furthermore, the cytoplasmic domain must now (in view of the claim amendments) comprise "a JAK binding site" (as noted in the section titled, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", it is unclear whether the JAK-binding site is found in part (1) or in the cytoplasmic domain as a whole). The claims specify that activation of the receptor is inhibited by the binding of a prey molecule, or a fusion protein comprising a prey molecule, to the heterologous bait polypeptide. Claim 1 and dependent claims 3-8, 11, 13 and 16 require that said fusion protein comprises a prey polypeptide and either an inhibitor of the activation of the receptor or a recruitment site for the inhibitor of the activation the receptor. Claim 22 only requires a prey polypeptide that interacts with the activation site to inhibit activation of the recombinant transmembrane receptor. Claims 1, 3, 6-8, 11, 13, 16 and 22 broadly encompass a receptor (or a vectors or cell encoding a receptor) comprising an ECD from any type of receptor; a cytoplasmic domain from any type of mammalian receptor (as long as a JAK-binding site is present); and any form of bait and prey polypeptide wherein the prey polypeptide, or fusion protein comprising a prey polypeptide, binding inhibits receptor

activation. Claims 4 and 5 limit the receptor to a homomultimerizing (claim 4) or heteromultimerizing receptor (claim 5). New claim 24 limits the "cytoplasmic domain of a mammalian receptor" to one that naturally comprises a JAK binding site. New claims 25 and 26 each limit the "inhibitor of activation" to one selected from a member of the SOCS family, a JAK phosphatase, and a STAT phosphatase.

The invention provides limited teachings regarding the nature of the receptor from which the cytoplasmic domain is derived. The only specific receptor cytoplasmic domain that is disclosed in the specification is derived from the leptin receptor. The specification teaches "a homomultimerizing recombinant leptin receptor with a heterologous bait polypeptide fused into or, preferentially, at the carboxyterminal end of its cytoplasmic domain" (pg 5, ¶ [0014]). The specification does not teach any other specific receptor cytoplasmic domains that can be used in the claimed recombinant receptor. Furthermore, all of the working examples in the specification that are directed to a recombinant receptor encompassed by the claims include a very specific derivative of the cytoplasmic domain of the leptin receptor. This derivative is designated LepRFFY (see pg 18, ¶ [0079] and pg 22, ¶ [0093]) and includes a leptin receptor cytoplasmic domain with a phenylalanine residue at position 985; a phenylalanine residue at position 1077; and a tyrosine residue at position 1138. Example 1 (pg 22) describes the "specific inhibition of activation of the EpoR-LepRFFY-EpoR by the SOC3-CISSH2 chimera is disrupted by overexpression of SOCS2" (pg 22, ¶ [0093]). In the recombinant receptor used this example (EpoR-LepRFFY-EpoR), the first EpoR is the extracellular ligand-binding domain; the LepRFFY is the cytoplasmic domain from a receptor including an activation site (the 'Y' that is residue 1138 in native LepR) and the second EpoR is the bait molecule. The SOCS3-CISSH2 is a fusion protein consisting of a CIS protein in which the SH2 domain of CIS (amino acids 82-218) is replaced with the SH2 domain of SOCS (amino acid residues 46-184; see pg 20, ¶ [0084]). The CIS portion is the binding partner (prey) for the bait molecule (the second EpoR) and the SOCS3 SH2 domain is an inhibitor of activation of the receptor. As taught in Eyckerman et al (2005), the LepRFFY "contains a functional Y1138 STAT3 recruitment motif and is therefore

signaling-competent, but it lacks the Y985 and Y1077 motifs required for recruitment of negative regulators" (pg 428 of Eyckerman et al, 2005. Nature Methods. 2(6): 427-433; cited previously). Example 1 further teaches that the recombinant receptor shows "very strong inhibition upon co-transfection of the chimeric SOCS3 CISSH2 protein. The SH2 domain targets the SOCS3 inhibitory regions towards the activated complex, resulting in specific inhibition" (pg 23, ¶ [00100]). Example 2 does not directly relate to the claimed receptor; instead it describes use of a recombinant receptor that is not encompassed by the claims to demonstrate that a specific bait-prey (ALK4-FKB12) interaction can be disrupted by the molecule FK506. In Example 3, ALK5 and FKB12 are used as bait and prey in the recombinant receptor and fusion protein from Example 1; in addition, a PTP-1B phosphatase domain is substituted for the inhibitory SOCS3 domain in the fusion protein. The specification further teaches that the inhibitor can be a "Suppressor of Cytokine Signalling (SOCS)" family member such as SOCS1 or SOCS3 (pg 7, ¶ [0018]). The specification further teaches that the inhibitor can be a "STAT phosphatase" or a "Protein Inhibitor of Activated STAT (PIAS), preferably PIAS3" (pg 7, ¶ [0019]).

In view of the teachings of the specification, the invention appears based on the following working model. Interaction between the bait molecule (part of the recombinant receptor) and the prey molecule (part of a fusion protein) allows the inhibitory molecule (also part of said fusion protein) to inhibit the activation site (1138Y) found in the cytoplasmic domain of the recombinant receptor. This inhibition occurs even if a ligand (e.g., Epo) binds to an extracellular ligand-bind domain (e.g., EpoR) of the recombinant receptor. However, if a second molecule is added (in addition to the ligand) that disrupts the bait-prey interaction, activation occurs because the inhibitory molecule is no longer recruited to the receptor to inhibit activation at the 1138Y residue (which functions as recruitment site for a STAT3 signaling molecule). The specification does not provide any teachings regarding specific receptors other than the leptin receptor, or any specific activation sites found in other receptors, that can be used in the recombinant receptor of the invention.

In the 10/5/07 response, Applicants submit that independent claims 1 and 22 have been amended to recite "wherein said cytoplasmic domain comprises at least a JAK binding site". Applicants argue that the specific examples of cytoplasmic domains provided in the specification are representative of a genus of "a very large and diverse field of possible cytoplasmic domains and indicate that there is little, other than a JAK binding site, that are required to function as claimed" (pg 6). Applicants point to example receptors made from EpoR and LepR in Examples 1 and 3 and argue that the low identity between the two sequences supports enablement of a genus of highly divergent cytoplasmic domains.

These arguments have been fully considered and are persuasive in part. While the specification does not describe any specific receptors with "a JAK binding site" other than the leptin receptor, the specification does teach a generic receptor with a cytoplasmic domain that comprises a "a JAK binding site" (pg 5). In contrast to Applicants' arguments, the Examiner can find no teaching in Example 1 or 3 wherein an EpoR cytoplasmic domain is used as the cytoplasmic domain of the receptor (as opposed to a ligand-binding domain or bait polypeptide). However, on further consideration of Applicants' arguments, and the relevant art, the Examiner finds persuasive the argument that the leptin receptor cytoplasmic domain is representative of a genus receptor cytoplasmic domains comprising JAK-binding sites that were well known in the art at the time of filing. For example, the reference (Ihle *et al*, 1995; cited above) referred to by Applicants on page 8 teaches that "mutational analysis of receptors that contain a single chain have shown that the cytoplasmic membrane-proximal region, which contains the box 1 and box 2 motifs, is required for receptor function. Both in vitro and in vivo studies show that this region is required for association of Jaks with cytokine receptors" (pg 70). Ihle *et al* further describe the genus of cytokine receptors comprising such JAK binding cites (see Figure 1 and pg 70). Furthermore, more recent relevant art also teaches, "Jaks associate with the membrane-proximal region of cytokine receptors. Amongst receptors, there is little homology except for short stretches called the box1 region, a proline-rich motif of eight amino acids, and the box2

region, a cluster of hydrophobic amino acid residues often followed by charged amino acids" (pg 1540 of Haan et al, 2006. Biochemical Pharmacology. 72: 1538-1546). In view of the teachings of the art at the time of filing, and as supported by post-filing date art, the specification at the time of filing provides enablement for the genus encompassed by "a JAK binding site" (i.e., a genus of JAK-binding sites each derived from a different cytokine receptor).

However, what is not found persuasive is that the added limitation (that the receptor must comprise a JAK-binding site) provides enablement for the full scope of the claims. The claimed recombinant receptor, while comprising "a JAK binding site", is not limited to naturally occurring cytokine receptor domains that include both a JAK binding site and an activation site that is a tyrosine residue that is phosphorylated upon activation. Instead, the claims encompass a vast genus of mammalian receptor cytoplasmic domains, including both cytokine receptors and structurally unrelated receptors (e.g., nuclear hormone receptors or G-protein coupled receptors (GPCRs)) that include a natural or artificial JAK binding site. Importantly, the genus of claimed recombinant receptors includes those with any type of "activation site". As set forth previously, the exact nature of the activation site on other receptors is not disclosed in the specification. The specification broadly defines "activation site" as "the site that, in the wild-type receptor, is modified after binding of a ligand to the ligand-binding domain, leading to a clustering and/or reorganization of the receptor and subsequent activation of the modifying enzyme activity and to which a compound of the signaling pathway can bind after modification, or any site that can fulfill a similar function" (pg 14). However, the only specific activation site described in the specification is a tyrosine phosphorylation site (e.g., pg 7; pg 11; Figure 1). Therefore, while the art appreciates a single type of activation site (a phosphorylated tyrosine residue) in a receptor that works with a JAK kinase, and the specification provides working examples related only to this single type of activation site, the claims encompass a vast genus of potential activation sites, includes sites that are activated by other post-translation modifications such as ubiquitination, acetylation, acylation, methylation, or glycosylation, and even sites

activated by a conformation change. Furthermore, the breadth of the encompassed "activation site" means that the "inhibitor of the activation" recited in the claim must be a corresponding inhibitor that functions to inhibit the activation site used in the receptor. However, the only specific inhibitors that are described in the specification are those that function in conjunction with the JAK kinase-tyrosine phosphorylation mechanism (specifically, SOCS family members, JAK phosphatases and STAT phosphatases). In view of the limited teachings of the specification and the prior art, the specification merely invites the skilled artisan to experiment in order to find an activation site other than a phosphorylated tyrosine and inhibitors other SOCS family members, JAK phosphatases and STAT phosphatases that will function in the claimed receptor.

As set forth previously, the instant specification suggests that a variety of inhibitors can be used in the fusion protein comprising a prey molecule and an inhibitor of activation, but the relevant art teaches unpredictability as to which inhibitors will actually function as inhibitors when used with a recombinant receptor comprising the LepRFFY cytoplasmic domain and a specific bait-prey combination. The instant specification demonstrates use of a fusion protein comprising a CIS protein in which the SH2 domain of CIS (amino acids 82-218) is replaced with the SH2 domain of SOCS3 (amino acid residues 46-184). This fusion protein was used to inhibit a recombinant receptor comprising LepRFFY as the cytoplasmic domain and EpoR residues 370-453 as the bait molecule; the CIS prey molecule binds to the EpoR bait molecule and allows the SOCS3 domain to inhibit LepRFFY activation. In view of this result, the specification suggests that the SOCS3 domain can be used as an inhibitor with any recombinant receptor. However, the relevant art shows that when a different bait-prey combination is used (FKBP12 and ALK4), many potential inhibitors fail to work. Specifically, Eyckerman et al (2005; cited above) teaches, "we generated fusion constructs of both FKBP12 and ALK4 with a variety of inhibitory domains derived from SOCS molecules, tyrosine phosphatases and PIAS molecules. All efforts with SOCS-based i-prey constructs proved unsuccessful. Inhibition via the kinase inhibitory regions of SOCS-1 and SOCS-3 may require a very specific context or orientation of these domains. Fusion

constructs with PIAS3 also did not have any inhibitory activity. In contrast, chimeric constructs containing the phosphatase domains of PTP-1B and TC-PTP (but not of SHP-1 or SHP-2) caused a substantial, specific reduction in signaling" (pg 429-430). Eyckerman further teaches that the phosphatase domain of PTP-1B works as inhibitor using a bait-prey combination that is MDM2-p53. However, another tyrosine phosphatase, TC-PTP, did not work with this combination of bait and prey. These teachings demonstrate that many inoperative embodiments will be found among the genus of receptors comprising a JAK-binding site, a tyrosine activation site and the disclosed inhibitors (SOCS family members, JAK phosphatases and STAT phosphatases). This points to the even greater level of difficulty in predicting and testing which other activation sites and corresponding inhibitors will work in the claimed invention in conjunction with receptors comprising JAK-binding sites.

The teaching of a single type of activation site (tyrosine residue), and a limited genus of inhibitors that are specific to said activation site, that can be used in the claimed receptor is not sufficient to enable the vast genus of potential engineered cytoplasmic domains that are encompassed by the claimed receptor. Due to the large quantity of experimentation necessary to generate the large number of recombinant receptors comprising other activation sites and other inhibitors and test such for activity, the lack of direction/guidance presented in the specification regarding other activation sites and inhibitors that will work in conjunction with a receptor comprising a JAK-binding site, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicants further argue that absolute predictability by the skilled artisan is not required to satisfy enablement, and that practicing the claimed invention may require extensive but not undue experimentation. Applicants point to two recent decisions as

supporting that extensive experimentation is not considered undue in the biotechnological arts (*Falkner v. Inglis* (2006) and *Ex parte Kublin* (2006)). Applicants argue that the skilled artisan could "create multiple receptors comprising a JAK binding site according to claim 1" and test these receptors using the procedures and examples outlined in the specification" (pg 6).

As described above, these arguments and the amendments to the claims, have been fully considered and are found persuasive in part. However, for the reasons set forth above the examiner maintains that undue rather than routine experimentation would be needed to practice the full scope of the invention with respect to the "activation site" and "inhibitor". With respect to *Falkner v. Inglis* (2006) and *Ex parte Kublin* (2006), the fact patterns in these cases are significantly different from the instant application and the decisions are not binding. Further, the concepts presented in the quotes from *Falkner v. Inglis* ("the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have to be considered undue in this art. Indeed great expenditures of time and effort were ordinary in the field") and *Ex parte Kublin* ("the amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those in the art") are not disputed; it is agreed that "difficult and time consuming" experimentation is not necessarily undue. In the instant case, the conclusion that practicing the full scope of the claimed invention would require undue experimentation is not based solely on "difficult and time consuming" experimentation, but rather on a *Wands* analysis that included: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. Importantly, in the instant case neither the prior art nor the specification provide any guidance as to what other activation sites and/or inhibitors to use in the claimed receptor, and the inventor would

not know where to even begin in selecting other components for the receptor. Thus, the experimentation would not be routine, but undue.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1, 3-8, 11, 13, 16, 22 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 9-12 of the 4/5/07 Office Action; new claims 24-26 are herewith included.

Applicants' arguments (10/5/07; pg 7-8), and the amendments to the claims, have been fully considered and are found persuasive in part. The rejection has been maintained but the rejection is maintained as set forth herein in view of Applicants' arguments, and the amendments to the claims. It is believed that all of Applicants' arguments are addressed below in the restated rejection.

In the response, Applicants submit that independent claims 1 and 22 have been amended to recite "wherein said cytoplasmic domain comprises at least a JAK binding site". Applicants argue that "JAK binding sites are well known in the art and that there is a disclosed correlation between structure and function for JAK binding sites". Applicants point to page 70 of Ihle et al (1995; cited above). Applicants argue that the recombinant receptor of the amended claims has a functional characteristic (comprising a JAK binding site) which has a well known correlation between structure and function. Applicants further argue that the specific examples of cytoplasmic domains provided in the specification are representative of a genus of "a very large and diverse field of possible cytoplasmic domains and indicate that there is little, other than a JAK binding site, that are required to function as claimed" (pg 8). Applicants point to example receptors made from EpoR and LepR in Examples 1 and 3 and argue that the low identity between the two sequences supports a written description of a genus of highly divergent cytoplasmic domains.

Applicants' arguments parallel those set forth in response to the enablement rejection. For reasons similar to those set forth above in the enablement rejection, it is found persuasive that the specification provides written description for a genus of receptors that comprise a JAK-binding site, a corresponding activation site that is a tyrosine residue, and that are inhibited by an inhibitor that is a SOCS family member, JAK or STAT phosphatase. However, the specification does not provide written description of recombinant receptors comprising other types of activation sites encompassed by the claims, or other types of inhibitors encompassed by the claims.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

The claims are genus claims because the claims are directed to variant recombinant receptors, and vectors and cells encoding said variant receptors. Each genus is highly variant because a significant number of structural differences between genus members are permitted. In particular, claims 1, 3-8, 11, 13, 16, 22 and 24-26 each encompass a receptor (or vector or cell encoding a receptor) comprising a cytoplasmic domain derived from any type of receptor and at least one activation site. As such, these claims encompass cytoplasmic domains from a vast array of structurally different receptors, including single transmembrane cytokine receptors as well as receptors without transmembrane domains (e.g., nuclear hormone receptors) or multiple transmembrane domains (e.g., G-protein coupled receptors). The only structural limitation is that the receptor must comprise a JAK-binding site.

The combination of the teachings in the specification and the prior art at the time of filing (described above in the enablement rejection), indicate support for possession of a genus of recombinant receptors comprising cytoplasmic domain derived from a cytokine receptor comprising a JAK-binding site. Such domains have a corresponding tyrosine activation site. Furthermore, the specification provides a written description of inhibitors of such activation sites (SOCS family member, JAK phosphatase and STAT phosphatases). However, the claims encompass receptors comprising structurally

unrelated activation sites and structurally unrelated inhibitors. The limited description in the specification does not indicate that Applicants had possession of the full range of such a genus at the time of filing.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of recombinant receptors. There is not even identification of the structure of activation sites that are not tyrosine residues, or inhibitors that are not SOCS family members or JAK or STAT phosphatases. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides, vectors and cells encompassed by the claims. Thus, no identifying characteristics or properties of the instant receptors are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the

'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only:

(1) a recombinant receptor comprising an extracellular ligand-binding domain of a mammalian receptor; a cytoplasmic domain comprising a domain derived from a cytoplasmic domain of a mammalian receptor, at least one activation site that is a tyrosine residue, and a heterologous bait polypeptide heterologous to the domain derived from a cytoplasmic domain of a mammalian receptor; wherein said cytoplasmic domain comprises a JAK-binding site; and wherein the activation of said recombinant receptor is inhibited by binding of a fusion protein to said bait polypeptide, said fusion protein comprising a prey polypeptide and an inhibitor of the activation of said recombinant receptor that is selected from the group consisting of a member of the SOCS family, a JAK phosphatase, and a STAT phosphatase, and

(2) vectors and cells encoding said receptor;

but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

New objections and/or rejections necessitated by Applicants' amendment

Claim Objections

Claims 1, 22 and 24 are objected to because of the following informalities:

(1) Claims 1, 22 and 24 recites the phrase "JAK binding site". However, the specification only uses the term "JAK-binding site" (i.e., JAK and binding are hyphenated). See, for example, paragraphs 12 and 14 of the specification.

(2) Claim 22 is also objected to for reciting a redundant word. Specifically, the amended claim recites "...comprising an intracellular domain derived from a mammalian receptor, a bait polypeptide, **and** an activation site, and a JAK binding site..." (the redundant word ("and") is emphasized here by representing it in bold-face). Applicants' amendment to claim 22 that adds "and a JAK binding site" renders the previous "and" redundant.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claims 24 and 26 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

New claims 24 and 26 were added 10/5/07. Claim 24 recites "The recombinant receptor of claim 1, wherein the cytoplasmic domain of a mammalian receptor naturally comprises a JAK binding site". Applicants' response indicates that basis for the new claims can be found "throughout the specification and more specifically at ¶ ¶ [0012], [0014], [0018], and [0019]". However, in contrast to Applicants' assertion the specification does not contain a description that invention includes the specific genus of recombinant receptors with a cytoplasmic domain of mammalian receptor that naturally comprises a JAK binding site. This specific genus would be distinguished from those that do not naturally comprise a JAK binding site; e.g., a cytoplasmic domain of a mammalian receptor that artificially comprises a JAK-binding site. However, the

specification does not distinguish between each specific genus as two different aspects of the invention. Instead, the specification (including paragraphs 12, 14, 18 and 19) only points to receptors comprising cytoplasmic domains that comprise a JAK-binding site in general (which includes natural or artificial JAK-binding sites). Therefore, the specification as originally filed lacks support for the genus of molecules encompassed by the new claim. Claim 26 depends from claim 24 and encompasses the same new matter.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-8, 11, 13, 16 and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended to recite "wherein said cytoplasmic domain comprises a JAK binding site". However, the antecedent basis of "said cytoplasmic domain" is unclear because the claim refers to two different cytoplasmic domains. The first is the "cytoplasmic domain" of the recombinant receptor and the second is the "cytoplasmic domain of a mammalian receptor" from which a domain is "derived" for use in the recombinant receptor. Therefore, it is unclear whether the "domain derived from a cytoplasmic domain of a mammalian receptor" is the only part that must comprise a JAK binding site, or whether the larger cytoplasmic domain of the recombinant receptor must comprise a JAK binding site (in which case the JAK binding site could be found in any part such as the "heterologous bait".

The remaining claims are rejected for depending from an indefinite claim.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646